Original Research

Making the Grade: The Impact of Low-Grade Toxicities on Patient Preference for Treatment With Novel Agents

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Abstract

Background: Targeted therapies have shown clinical benefit in the treatment of solid tumors. The toxicity profiles and treatment duration and schedule of these agents differ considerably from those of traditional chemotherapy. Many studies of targeted therapies report sizeable numbers of grade 1 or 2 toxicities. We sought to determine whether anticipation of low-grade toxicities and treatment logistics impact patient willingness to undergo therapy. **Patients and Methods:** A total of 209 patients with cancer (101 lung and 108 breast) were surveyed at the Vanderbilt-Ingram Cancer Center regarding willingness to comply with treatment based on anticipated efficacy, dosing convenience, and toxicity profiles. All toxicities were Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade 1 and 2. Willingness to comply with treatment depending on toxicity, anticipated benefit, cancer type, and dosing convenience was compared. **Results:** A substantial number of patients (2.9%–48.8%, depending on the toxicity described) professed unwillingness to undergo treatment because of anticipated grade 1 and 2 toxicities. Gastrointestinal and constitutional toxicities had a stronger negative impact on patient willingness to undergo therapy than dermatologic toxicity. Patients with lung cancer were significantly more likely to accept dermatologic and gastrointestinal toxicities than those with breast cancer. Willingness to tolerate toxicities correlated with expected benefit in terms of life expectancy and chance of cure. Lengthy travel distance for treatment negatively impacted willingness to undergo treatment. **Conclusions:** Anticipation of low-grade toxicities and dosing inconvenience negatively impacts patient willingness to be treated, which may affect adherence and therapeutic outcomes from therapy. Long-term tolerability should be considered when developing and assessing the impact of novel agents. (J Natl Compr Canc Netw 2015;13:1490–1495)

Background

Cancer is the second leading cause of mortality in the United States, with 1,658,370 new cancer cases and 589,430 cancer deaths anticipated in 2015.[1] A multitude of targeted therapies have shown clinical benefit in the treatment of patients with a wide range of solid tumors. These targeted therapies are increasingly being adopted as the standard of care. The route, frequency, and duration of administration of these agents as well as their toxicity profiles differ significantly from traditional cytotoxic chemotherapy. Studies of targeted therapies commonly report so-called low-grade (Common Terminology Criteria for Adverse Events [CTCAE] grade 1 and 2) toxicities that can affect up to 75% of treated patients.[2–4] Although most physicians may not consider these toxicities prohibitive to treatment, low-grade adverse events (AEs) may negatively affect quality of life and patient compliance with therapy. Additionally, because of differences in their metabolism and mechanism of action, many of these agents require once- or twice-daily oral administration, or weekly intravenous administration, which requires patient adherence for optimal

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effectiveness. The impact of low-grade AEs and the frequency of drug administration on patient willingness to undergo treatment has been underexplored in patients with cancer.

Treatment adherence is vital to therapeutic efficacy. Prior studies in patients with cancer have found that symptomatic AEs are an important contributor to treatment noncompliance, discontinuation, or dose reduction.[5–7] However, there may be differences in what patients and physicians perceive as problematic AEs. Prior studies have shown that physicians underreport the incidence and severity of symptoms compared with patients' direct reports,[8–10] and that patient reports provide a more accurate picture of overall health status.[11,12] Evidence indicates that patients seek out treatment approaches that are manageable, tolerable, and, in their opinion, effective,[13] but the impact of low-grade toxicity or frequent dosing schedules on patient perceptions of efficacy and tolerability is not clear. This study used a one-time survey to investigate the impact of low-grade (CTCAE grade 1 and 2) toxicities, convenience (ie, frequency of dosing, whether travel for treatment is required), and perceived treatment efficacy on patient willingness to adhere to therapy. The toxicities presented to patients were those most commonly associated with targeted agents currently on the market or under development, and were based on the CTCAE version 4.0 grade 1 and 2 descriptions.

Patients and Methods

All English-speaking patients with lung or breast cancer seen by medical oncologists at Vanderbilt-Ingram Cancer Center were eligible to participate. Potential participants were identified by attending physicians in clinic and then approached by a member of the research team not directly involved in their care to ask whether they would be willing to answer a one-time questionnaire. Written informed consent was obtained from each participant. Questionnaires were administered in private rooms at the cancer center. Patients were recruited between July 2012 and August 2013. A member of the research team was available on-site should a patient require clarification about any item on the survey. This study was approved by the Vanderbilt University Institutional Review Board.

The survey instrument was developed by the research team (see supplemental eAppendix 1, available with this article at JNCCN.org). A total of 7 demographic variables and 9 nondemographic variables were included. Patients were asked to rate their willingness to receive treatment in various hypothetical scenarios that were devised to pair increasing scales of potential benefit with descriptions of toxicity and schedule inconvenience. The description of expected benefit ranged from palliative intent with an expected increased survival of 3 to 6, 6 to 12, or greater than 12 months to curative intent requiring either less than or greater than 12 months of treatment. Patients were then asked to rate willingness to be treated on a 1- to 5-point Likert scale (1 = very unlikely; 5 = very likely) if also expected to experience a particular toxicity while receiving the hypothetical treatment benefit. Nine categories of dermatologic, gastrointestinal, or constitutional toxicities common to novel agents were included, all of which were CTCAE version 4.0 grade 1 or 2 in description. The impact of dosing schedule and convenience was also assessed by asking patients to rate willingness to be treated with either palliative or curative intent under various scenarios of dosing frequency (twice weekly, weekly, every 2 weeks, or every 3 weeks) and required travel distance for treatment (<25 or >25 miles). Data were de-identified and entered into a secured electronic database (REDCap) by investigators.

Statistical Analyses

Descriptive summaries of the demographic and cancer history data were performed. Categorical variables were tabulated, and means were calculated for continuous variables. We used multivariable ordinal logistic regression under a proportional odds model to compare differences in willingness to receive treatment affected by perceived efficacy of treatment (anticipated benefit) and different classes of toxicities (dermatologic, gastrointestinal, or constitutional), as well as between patients with breast versus lung cancer, adjusting for education level, employment status, identified primary caregiver, treatment history (0–1 vs ≥2 prior therapies), and current stage. The last 2 models also included adjustments for anticipated benefit and toxicity grades. Anticipated benefit was grouped in 5 ordered categories (3–6 months treatable, 6–12 months treatable, >12 months treatable, >12 months curable, and <12 months curable). The last 2 models included adjustments for anticipated benefit and toxicity grades. Binary logistic regression

was performed to compare willingness to receive treatment between short and long driving distances. We adjusted for correlated responses within each class of toxicity using the generalized estimating equation approach, robust covariance matrix. Statistical analyses were conducted with R version 3.1.2.

Results

Of the 209 patients who completed the survey, 101 (48%) had lung cancer and 108 (52%) had breast cancer. The average age was 58.4 years, and 159 patients (76%) were female. A total of 127 patients (61%) indicated that their spouse was their primary caregiver, and 125 patients (59%) required assistance with transportation to the cancer center for treatment. Most patients (92%) had received at least 1 prior line of therapy, and 66 patients (32%) had received 4 or more lines of therapy. Further demographics data are presented in supplemental eTable 1.

A substantial number of patients (range, 2.9%–48.8%) stated they would be deterred from treatment if they expected to experience a particular toxicity. Willingness to receive treatment was significantly associated with anticipated benefit for both grade 1 (Figure 1) and grade 2 (Figure 2) toxicities. Patients were less willing to tolerate chronic low-grade toxicity if treatment were described as palliative with a smaller degree of potential benefit. For example, 13.5%, 15.9%, and 18.4% of patients would be unwilling to tolerate chronic grade 1 diarrhea if treated with palliative intent with an expected benefit of greater than 12 months, 6 to 12 months, or 3 to 6 months, respectively (odds ratio [OR] for anticipated benefit, 1.24; $P<.0001$). In contrast, only 8.7% of patients would be unwilling to tolerate chronic grade 1 diarrhea if treated with curative intent for less than 12 months. Gastrointestinal and constitutional toxicity had a stronger negative impact on patient willingness to undergo treatment, compared with dermatologic toxicity ($P<.0001$; OR for gastrointestinal vs dermatologic, 0.58; 95% CI, 0.53–0.68; OR for constitutional vs dermatologic, 0.86; 95% CI, 0.79–0.94), adjusted for anticipated benefit and toxicity grades. For example, 32.5% of patients stated they would decline curative intent treatment if grade 2 vomiting were expected versus 10.6% if grade 2 rash were expected. Fatigue also had a strong impact on patient preference for treatment, with grade 2 fatigue causing 30.4% of patients to decline treatment

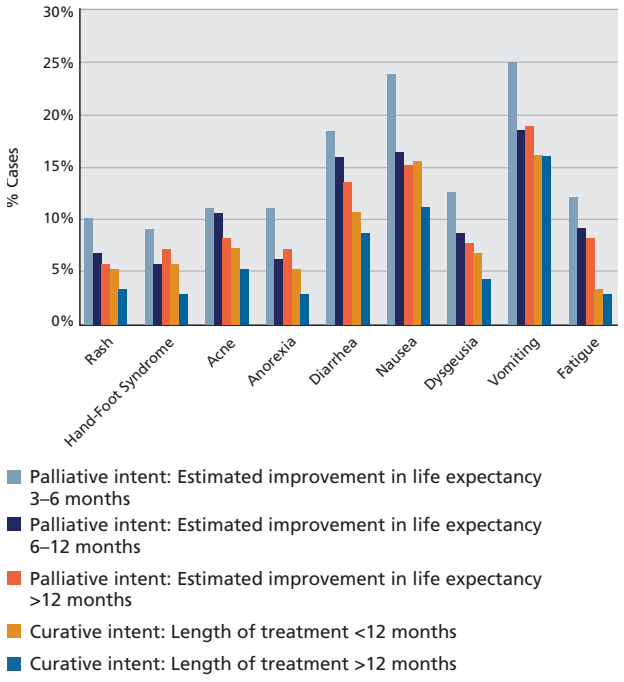

Figure 1 Percentage of patients who stated that they would be unwilling to adhere to treatment by anticipated benefit and grade 1 toxicity. For each toxicity described, willingness to be treated was associated with potential benefit ($P<.001$).

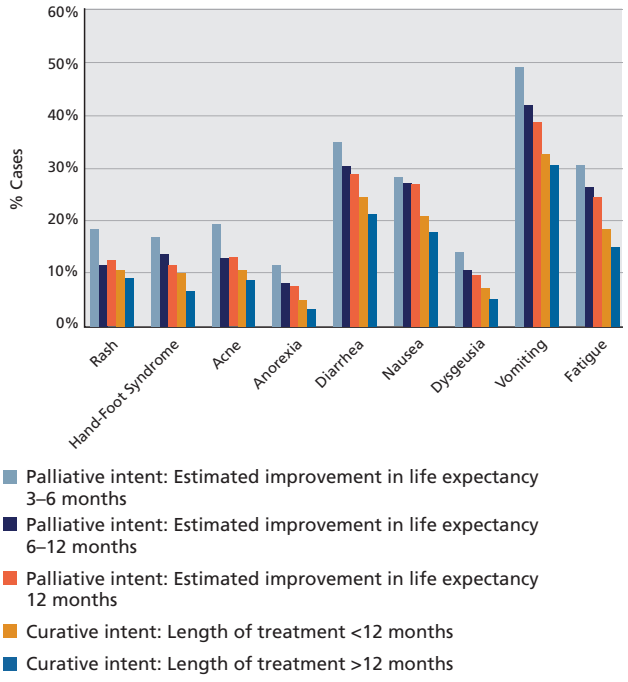

Figure 2 Percentage of patients who stated that they would be unwilling to adhere to treatment by anticipated benefit and grade 2 toxicity. For each toxicity described, willingness to be treated was associated with potential benefit ($P<.001$).

with a short-term palliative benefit (3–6 months) and 18.5% of patients to decline potentially curative treatment. No significant difference was noted in patient willingness to receive treatment in anticipation of gastrointestinal versus constitutional toxicity.

Patients with lung cancer were more willing to receive treatment than those with breast cancer when asked about dermatologic toxicities (P=.0518; OR for patients with breast vs lung cancer, 1.61; 95% CI, 1.00–2.61) and gastrointestinal toxicities (P=.0738; OR for patients with breast vs lung cancer, 1.5, 95% CI, 0.96–2.34), although this was with marginal statistical significance. No significant difference was seen between patients with breast versus lung cancer regarding willingness to undergo treatment based on distance or dosage frequency.

No difference was noted in willingness to be treated with anticipation of any category of toxicity between patients who had received 0 to 1 lines of treatment compared with those who had received 2 lines or greater.

Requirement to travel a lengthy distance (>25 miles) for intravenous therapy had a significant negative impact on willingness to be treated, depending on the frequency of travel (see supplemental eTable 2). Patients were less willing to be treated if therapy required travel of more than 25 miles compared with a shorter distance of travel, whether the goal of treatment was curative or palliative. However, if travel frequency were every 3 weeks, then distance did not appear to have a significant impact on willingness to be treated.

Discussion

In this cross-sectional study of lung and breast cancer patients, grade 1 and 2 toxicities had a negative impact on the likelihood that patients would be willing to undergo therapy. Willingness to be treated varied according to type of toxicity; anticipation of gastrointestinal toxicity and fatigue had a stronger impact on patient willingness to be treated than dermatologic toxicity. Number of prior therapies did not impact patient willingness to undergo treatment, suggesting that has a neutral effect on patient anticipation of future treatment toxicity. Greater potential benefit mitigated the negative impact of toxicity on patient willingness to be treated, with more patients likely to accept toxicity if the potential survival benefit were higher. This finding is similar to data relating to nononcologic therapies, which show that perceived treatment efficacy increases the likelihood of adherence.[14–17] However, even if the outcome were potential cure, more than 20% of patients stated they would decline treatment if it were at the cost of experiencing grade 2 toxicities of nausea, vomiting, or diarrhea on a chronic basis, and more than 15% would decline potentially curative treatment if faced with chronic grade 1 nausea, vomiting, or diarrhea. Thus, it may be that certain types of chronic toxicity, even if "low-grade," impair quality of life to a degree that some patients are deterred from treatment. In clinical practice, poor quality of life could lead to treatment refusal, noncompliance, dose reductions, or treatment "breaks," which may affect overall efficacy.

Targeted therapies are becoming an increasingly important tool in the treatment of cancer, leading to improved patient outcomes and survival. However, the toxicity profiles of these agents differ significantly from traditional cytotoxic chemotherapy, with patients often experiencing chronic, low-grade toxicity. For instance, the epidermal growth factor receptor tyrosine kinase inhibitors erlotinib and gefitinib are associated with high rates of dermatologic and gastrointestinal side effects. Up to 75% of patients on erlotinib and 33% of patients on gefitinib report rash, and diarrhea occurs in up to 55% and 35% of patients on erlotinib and gefitinib, respectively.[3,18,19] One cross-sectional study of multiple targeted therapies found that 76% of patients reported symptomatic side effects of any grade.[20] Patients on targeted therapies may also experience multiple toxicities simultaneously, further impairing quality of life and potentially leading to dose reductions or even drug discontinuation.

Although chemotherapy has traditionally been given as cyclic intravenous infusions in the cancer clinic, most targeted therapies require frequent oral or intravenous administration and are given continuously as long as the patient is deriving benefit, which may potentially extend for years. This paradigm shift of treating cancer similarly to other chronic diseases has led to improved outcomes for patients. However, processes that establish optimal drug dosing for patients with cancer have not had a comparable shift in how treatment toxicities are assessed and valued. The recommended doses for targeted agents are typi-

cally derived according to the same algorithm as traditional cytotoxic chemotherapy, in which severe (grade 3 and 4) toxicity is considered dose-limiting, but low-grade toxicity is not always viewed with the same weight. Although low-grade toxicities may not pose the same immediate safety threat as grade 3 and 4 AEs, they do play an important role in the overall tolerability of treatment and may influence both patient willingness to undergo treatment and adherence to a given treatment regimen due to negative impact on quality of life. Frequent dosing schedules may also be problematic for patients who must travel to receive intravenous treatment, and this inconvenience may deter some patients from treatment or lead to treatment "breaks" for others. Noncompliance with therapy may affect efficacy.

Although this study prospectively evaluates patient willingness to undergo treatment rather than actual adherence rates, it is notable that anticipation of low-grade toxicity had a strong effect on initial interest in treatment and suggests that chronic low-grade toxicities could impact treatment adherence. Although medical providers may assume that patients with a life-threatening illness such as cancer are adherent to their treatment plan,[21,22] prior studies have found a wide variation in adherence rates to oral anticancer therapies, ranging from 16% to 100%.[20,23,24] AEs have been cited as the reason for drug discontinuation in up to 34% of patients taking oral anticancer agents.[23] Our study suggests that even low-grade toxicities may have a high impact when expected to be experienced on a long-term basis. Patient education, expectant management of toxicity, and continual assessment of patient adherence are likely to improve patient compliance and treatment tolerability.

This study was conducted at a single institution on a select group of patients with cancer. Although prior lines of therapy were captured, the type of therapy or history of prior treatment toxicity was not. The survey instrument was designed using hypothetical scenarios to allow for direct assessment of multiple toxicities and degrees of potential benefit, and it should be recognized that individual real-world situations are inherently more complex. Most patients surveyed were previously treated. Although it is possible that results may differ with a treatment-naïve population, no relationship was seen between number of prior treatments and willingness to adhere to treatment among the patients in this study.

Conclusions

The increasing use of targeted therapies is steadily shifting the paradigm of cancer care from an acute illness to a chronic disease model in many solid tumor malignancies. Because patient willingness to adhere to their treatment plan outside of the clinic setting is both crucial to the efficacy of treatment and difficult to observe, the creation of therapeutic regimens that are not only effective but also readily tolerated is critical to treatment success. This study suggests that low-grade toxicities that may have been deemed acceptable for a limited period may be perceived as onerous by patients when expected on a long-term basis, potentially affecting adherence and outcomes. The conventional model for assessing the efficacy of new agents typically focuses on grade 3 and 4 toxicities, which are often acutely experienced, rather than low-grade toxicities, which may be both chronic and cumulative. Just as novel therapies have elevated expectations for survival in cancer care, the bar should also be raised when assessing the overall tolerability of targeted agents in development.

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References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
2. Ravaud A. Treatment-associated adverse event management in the advanced renal cell carcinoma patient treated with targeted therapies. Oncologist 2011;16(Suppl 2):32–44.
3. Cataldo VD, Gibbons DL, Perez-Soler R, Quintas-Cardama A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. N Engl J Med 2011;364:947–55.
4. Aapro M, Andre F, Blackwell K, et al. Adverse event management in patients with advanced cancer receiving oral everolimus: focus on breast cancer. Ann Oncol 2014;25:763–773.
5. Bhattacharya D, Easthall C, Willoughby KA, et al. Capecitabine non-adherence: exploration of magnitude, nature and contributing factors. J Oncol Pharm Pract 2012;18:333–342.
6. Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. Leuk Res 2011;35:626–630.
7. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol 2010;28:2381–2388.
8. Pakhomov SV, Jacobsen SJ, Chute CG, Roger VL. Agreement between patient-reported symptoms and their documentation in the medical record. Am J Manag Care 2008;14:530–539.
9. Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 2004;22:3485–3490.

10. Basch E. The missing voice of patients in drug-safety reporting. N Engl J MEd 2010;362:865–869.
11. Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. J Natl Cancer Inst 2011;103:1851–1858.
12. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 2009;101:1624–1632.
13. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther 2001;26:331–342.
14. Hilliard ME, Eakin MN, Borrelli B, et al. Medication beliefs mediate between depressive symptoms and medication adherence in cystic fibrosis. Health Psychol 2015;34:496–504.
15. Sweileh WM, Zyoud SH, Abu Nab'a RJ, et al. Influence of patients' disease knowledge and beliefs about medicines on medication adherence: findings from a cross-sectional survey among patients with type 2 diabetes mellitus in Palestine. BMC Public Health 2014;14:94.
16. Hugon A, Roustit M, Lehmann A, et al. Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. Transplantation 2014;98:222–228.
17. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? BMC Health Serv Res 2012;12:98.
18. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–132.
19. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–957.
20. Barthelemy P, Asmane-De la Porte I, Meyer N, et al. Adherence and patients' attitudes to oral anticancer drugs: a prospective series of 201 patients focusing on targeted therapies. Oncology 2014;88:1–8.
21. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst 2002;94:652–661.
22. Nilsson JL, Andersson K, Bergkvist A, et al. Refill adherence to repeat prescriptions of cancer drugs to ambulatory patients. Eur J Cancer Care (Engl) 2006;15:235–237.
23. Timmers L, Boons CC, Kropff F, et al. Adherence and patients' experiences with the use of oral anticancer agents. Acta Oncol 2014;53:259–267.
24. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin 2009;59:56–66.

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